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Scientific Update™

Systolic Hypertension in the Elderly: the Systolic Hypertension in Europe Trial (Syst-Eur)

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The field of cardiovascular medicine, particularly the study of hypertension, was shaken in the recent past by the controversy in the medical and lay media about the safety of calcium antagonists. This controversy was fuelled by reports based on observational studies, such as case-control and cohort studies, that putatively indicated that calcium antagonists increased the risk of coronary heart disease,[1,2] cancer,[3,4] and bleeding.[4-9] Following this controversy, the Liaison Committee of the World Health Organization and the International Society of Hypertension formed an ad hoc subcommittee to review the relevant, available evidence linking calcium antagonists to those risks. Recently, the subcommittee issued its conclusions, the highlights of which can be summarized as follows[10]:

1) ***"The available evidence does not prove the existence of either beneficial or harmful effects of calcium antagonists on the risks of major coronary heart disease events, including fatal or non-fatal myocardial infarctions and other deaths from coronary heart disease. This applies to the evidence on all calcium antagonists considered collectively; and to that on subgroups of these agents.."***

2) ***"...The available evidence from observational studies does not provide good evidence of an adverse effect of calcium antagonists on cancer risk..."***

3) ***"...The available evidence from observational studies and randomized trials does not provide clear evidence of an adverse effect of calcium antagonists on bleeding risk".***

Following the resolution of this controversy, the field of hypertension research is now in an excellent position to start providing answers to a number of questions of crucial importance to the clinician, such as whether newer agents, including calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-II receptor antagonists, are equivalent or better than more traditional agents, such as beta-blockers and diuretics. These agents have demonstrated in prospective, randomized trials to reduce the incidence of important cardiovascular events, such as stroke and myocardial infarction, in hypertensive patients. Another equally important yet unresolved question is the optimal level of diastolic blood pressure control. In other words, is it "the lower the better" or will a "J curve" effect limit the benefits of more aggressive blood pressure control? Other critical issues, in view of our aging population and the overwhelming impact of cerebrovascular and coronary disease on our health-care resources, include a better understanding of the criteria for and the benefits of management of systolic hypertension in the elderly, including the impact of antihypertensive therapy on the preservation of cognitive function and quality of life.

The unfortunate controversy about the safety of calcium antagonists underscores two major issues: the importance of large-scale, prospective, randomized trials, which are irreplaceable in providing information. These trials identify not only the benefits of an intervention in modifying the incidence of prespecified endpoints but in establishing the safety of that intervention, pharmacological or otherwise; and, the role that observational studies play in generating public concern, despite serious limitations that need to be re-emphasized. It is clear that these studies are plagued by serious deficiencies, which include but are not

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limited to detection and publication bias, since negative findings are less likely to be published than positive ones.

Ongoing trials

Within the next few years, data will be available from trials involving about 100,000 hypertensive patients randomized to a calcium antagonist or traditional beta-blocker/diuretic-based therapy. These prospective studies should provide additional reliable data on the long-term safety of calcium antagonists. Of note, most of these studies had been planned or initiated – in some cases, recruitment had been completed prior to the controversy.

An important ongoing study that should be reported soon is STOP-Hypertension II. This study compares the newer antihypertensive strategies based on calcium antagonists or ACE inhibitors with more traditional beta-blocker/diuretic-based treatment. It was designed as a follow-up to STOP-Hypertension,[11] a study published in 1991, which was based on 1,600 hypertensive patients between the ages of 70 and 85 who were randomized to active treatment with beta-blockers or diuretics compared to placebo.

In STOP-Hypertension, the active treatment resulted in a mean decrease in blood pressure of 19.5/8.1 mm Hg (systolic/diastolic) relative to the placebo group[12]. This reduction of blood pressure was associated with a number of significant outcomes, primarily a decrease of 40% (p=0.003) in all primary endpoints combined (fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and all-cause mortality). Independently, fatal and non-fatal stroke was decreased by 47% and total mortality by 43%.

The strongly positive results of STOP-Hypertension provided the impetus for the continuation of these investigations and the design of STOP-Hypertension II, a trial in elderly hypertensives (ages 70-85) that is testing whether new treatment strategies with calcium antagonists or ACE inhibitors are equivalent or better than the treatment already shown to be effective in the first trial in reducing cardiovascular mortality and morbidity. This new trial used the same blood pressure criteria as the first one (>189/105 mm Hg) and randomized patients to treatment with beta-blocker + diuretic, ACE inhibitor (lisinopril) + diuretic, or calcium antagonist (felodipine, isradipine) + ACE inhibitor. A total of 6,628 patients were randomized between September 1992 and the end of recruitment in December, 1994. The study is conducted at 312 centers in Sweden. Its statistical power is based on reaching 485 fatal cardiovascular endpoints. Very important conclusions are expected of this direct comparison of the old and new in antihypertensive therapy.

Syst-Eur: a landmark study

Syst-Eur was reported at the recent annual meeting of the European Society of Hypertension in Milan, Italy, where it was definitely the highlight of the meeting. Its impact is likely to be highly significant in clinical practice. The principal aim of the study was to evaluate whether treatment of isolated systolic hypertension in the elderly decreases the incidence of stroke. Syst-Eur was a prospective, double-blind, placebo-controlled, randomized trial of therapy of systolic hypertension in the elderly based on the calcium antagonist nitrendipine, a dihydropyridine, and the subsequent, stepwise addition of the ACE inhibitor enalapril and the diuretic hydrochlorothiazide.

The trial was initiated in 1989, the last patient was randomized in January, 1997. Based on analysis by the Data Safety Monitoring Committee at the prespecified endpoint of 100 strokes, the trial was stopped long before the end of the scheduled follow-up period, when data revealed a striking 42% reduction in the primary endpoint of fatal and non-fatal strokes (p=0.003) with the active nitrendipine-based treatment.

Study design[11]

Following a 3-month, single-blind, placebo run-in phase, when the diagnosis of isolated systolic hypertension was confirmed and patients were characterized for the presence or absence of pre-existing cardiovascular complications, patients were randomized to active treatment or placebo. Patients could leave this double-blind phase of the trial if they experienced a fatal complication or another primary endpoint. After such an occurrence, patients proceeded to the supervised open follow-up phase, where they continued to be closely monitored at regular intervals, which allowed the most rigorous intention-to-treat analysis. As mentioned, the first-line therapy was the calcium antagonist nitrendipine, starting at 10 mg once daily and titrated as needed to 10 mg twice daily to a maximum of 20 mg once daily. The second-line therapy was nitrendipine plus enalapril. The latter was started at 5 mg once daily and titrated to 10 mg once daily to a maximum of 20 mg once daily. The third-line therapy was the addition of hydrochlorothiazide at 12.5 mg once daily with possible titration to a maximum of 25 mg once daily. The medications or their matching placebos were combined and titrated to achieve the goal of a sitting systolic blood pressure <150 mm Hg and a decrease in systolic blood pressure of at least 20 mm Hg compared to baseline values (Table 1).

Patient characteristics

A total of 8,928 patients were screened for possible enrollment. Of these, 74% entered the run-in phase and 4,695 (53% of the screened population) were randomized to the double-blind phase of the study. The patients were enrolled by 198 centers in Europe and Israel. A total of 75% of centers and 55% of patients were from 12 countries in Europe and Israel, whereas 25% of centers and 45% of patients were from 10 countries in Eastern

Table 1: INCLUSION CRITERIA

Age ≥ 60 years
Sitting systolic blood pressure 160-219 mm Hg
Diastolic blood pressure <95 mm Hg
Standing blood pressure >140 mm Hg (to exclude patients with orthostatic hypotension).

Europe. The patients were very well-matched in their baseline characteristics, as can be seen in Table 2.

As further evidence of the excellent randomization process, there were no differences in body mass index, serum cholesterol levels, previous antihypertensive therapy, alcohol intake, or any of the other baseline characteristics. In terms of the systolic blood pressure on entry, 41% of patients had a sitting systolic blood pressure in the range of 160-170 mm Hg – levels commonly found in clinical practice in this population – whereas 35% had a systolic blood pressure between 170-180 mm Hg and only 2% had levels higher than 200 mm Hg.

Table 2: BASELINE CHARACTERISTICS

	Placebo (n=2297)	Active treatment (n=2398)
Age (mean)	70.2 y	70.3 y
Blood pressure (sitting)	174/85 mm Hg	174/85 mm Hg
Systolic BP (standing)	169 mm Hg	169 mm Hg
% women	66.2	67.5
Cardiovascular complications (%)*	30.3	29.4
Current smokers (%)	7	7

(*cardiovascular conditions present at entry: Left ventricular hypertrophy by EKG, 13.1%; signs or symptoms consistent with coronary heart disease, 12.2% – including 3.5% with previous MI ; signs or symptoms of cerebrovascular disease, 2.2% – including 1% previous stroke; other cardiovascular conditions, 2.3%).

Blood pressure control

In total, the study provided for 11,704 pt-years of observation. Mean follow-up at trial cessation was 2 years. The blood pressure-lowering differential between the two strategies became obvious shortly after initiation of the double-blind phase (< 3 months), stabilized at 6 months, and was maintained throughout the remainder of the study. The analysis by intention-to-treat showed that the systolic blood pressure was significantly lower in the nitrendipine group by 10±4 (8.8, 11.4) mm Hg at 2 years and 10.7±5 (8.4,12.5) mm Hg at 4 years [mean difference, (95% confidence intervals)]. The proportion of patients on active treatment was greater than 80% during follow-up. Enalapril was needed in only 33% of patients (mean dose 15 mg/day) and hydrochlorothiazide use was in the range of 9-24% of the patients (mean dose, 20 mg/day). Thus, nitrendipine was highly effective as monotherapy in the majority of patients and was very well-tolerated over a long period of time.

Results of Syst-Eur (Table 3)

The curves for all major predefined endpoints, including stroke, started to diverge between the active treatment and placebo groups very early and, importantly, continued to diverge during the rest of the follow-up period. As mentioned, for the major endpoint of fatal and non-fatal stroke, there was a striking reduction of 42% in the actively treated group (p=0.003).

Other minor cardiovascular endpoints also favored the active treatment group with a decrease in transient ischemic attacks of 12% (p=0.062); angina pectoris, 24% (p=0.04); and peripheral vascular disease, 32% (p=0.08) as shown in Table 3. The analysis of non-cardiovascular endpoints yielded important results, particularly in view of the recent controversy. The incidence of bleeding (excluding cerebral hemorrhage and retinal bleeding) was insignificantly lower in the active treatment group (-10%, p=0.74), as was fatal and non-fatal cancer (-15%, p=0.29).

Benefits of active treatment in Syst-Eur

Further analysis of data leads to the conclusion that treatment of 1,000 patients for 5 years with the Syst-Eur protocol would lead to the prevention of 29 strokes and 53 major cardiovascular endpoints. A comparison of Syst-Eur with other trials of either isolated systolic or combined systolic/diastolic hypertension shows very consistent results in terms of relative or absolute benefits. For instance, the prevention of fatal and non-fatal stroke by antihypertensive therapy was similar between Syst-Eur and SHEP[13] . As well, an analysis of prevention of cardiovascular mortality results in almost identical numbers of deaths prevented by treating 1,000 patients for one year (4 in Syst-Eur, 3 in STOP, and 2 in SHEP). However, it is important to emphasize that SHEP included a more selected population of hypertensive elderly patients, as 447,921 patients were screened in order to recruit the final study population of 4,736. In contrast, 53% of screened patients were enrolled in the double-blind phase of Syst-Eur. Arguably, the results of Syst-Eur observed in 22 different countries would be more easily extrapolated to clinical practice and more applicable to the elderly population at large.

Additionally, Syst-Eur included a substudy called the Syst-Eur Vascular Dementia Project (SE-VDP), which was designed to assess and follow the evolution of cognitive functions and to determine the influence of antihypertensive therapy in the elderly. This substudy set out to test one of the more interesting and novel hypotheses in hypertension research: that antihyper-

Table 3: IMPACT OF ACTIVE TREATMENT ON MAJOR ENDPOINTS

	% decrease	p value
Combined fatal/non-fatal cardiovascular endpoints	-32%	<0.001
Fatal/non-fatal stroke	-42%	0.003
Non-fatal stroke	-44%	0.007
Fatal/non-fatal cardiac events	-26%	0.03
Non-fatal cardiac events	-33%	0.03
Cardiovascular mortality	-27%	0.07
MI mortality	-56%	0.08
Non-cardiovascular mortality	-1%	0.95
Total mortality	-14%	0.22

tensive therapy not only prevents major cardiovascular endpoints but can prevent the deterioration of cognitive function. A total of 2,225 elderly hypertensive patients without dementia (1,374 women and 751 men), with baseline characteristics indistinguishable from the complete Syst-Eur population, were enrolled in the SE-VDP substudy. The determinants of cognitive impairment increased 9% for year of age and decreased 20% for each year of education. Interestingly, cognitive impairment was correlated with systolic blood pressure (r=-0.08 in men and -0.10 in women, $p<0.01$) but not with diastolic blood pressure (r=0.04 and 0.05, p=not significant). Further analyses to determine the influence of the different treatment strategies are underway.

Principal conclusion of Syst-Eur

Stepwise antihypertensive treatment started with nitrendipine reduces the incidence of stroke and cardiovascular complications in elderly patients (> 60 years of age) with isolated systolic hypertension.

The Systolic Hypertension in China Trial (Syst-China)

This study was conducted in China and was quite similar in design to Syst-Eur. It addressed the important question of the role of treatment of isolated systolic hypertension in the elderly in the prevention of stroke. The principal inclusion criteria are identical to Syst-Eur: patients ≥ 60 years of age, sitting blood pressure between 160-219 mm Hg, standing blood pressure >140 mm Hg, and diastolic blood pressure < 95 mm Hg. SYST-China also includes a 3-month placebo run-in period followed by a randomized, placebo-controlled phase of 5-7 years. The first-line therapy is based on nitrendipine, second-line therapy on captopril, and third-line therapy is the addition of hydrochlorothiazide. The targets of the study are a sitting systolic blood pressure <150 mm Hg and a systolic blood pressure reduction > 20 mm Hg.

There are some differences in the baseline characteristics compared to Syst-Eur. There were 2,379 patients enrolled in the placebo-controlled phase of Syst-China (1,134 in the placebo group and 1,245 on active treatment), the mean age was younger than in the European study (66.7 years for the placebo group, 66.4 years in the active treatment group), and there were significantly less women (34.9% and 36.4%, respectively) and more current smokers (34.5% and 30.5%, respectively). At present, all centers have completed the follow-up of patients, the quality check of data is being conducted, and the analysis of endpoints is in progress.

Summary

Now that the controversy about the safety of calcium antagonists has subsided, the field of hypertension research can move on to answer some important questions and test novel hypotheses. Ongoing studies will provide information, over the next few years, on whether new and generally better tolerated treatment strategies, such as calcium antagonists, ACE inhibitors, and angiotensin-II receptor antagonists are better than the traditional approach based on beta-blockers and diuretics. As well, novel information will become available on the effects of antihypertensive therapy on cognitive function, mood, and quality of life. The optimal level of diastolic blood pressure control is currently being investigated in a large, international, multicenter trial.

Some critical answers have started to emerge. The release of the results of the Syst-Eur trial constitute a landmark in the management of isolated systolic hypertension in the elderly. Nitrendipine was safe and highly effective in improving the outcome of elderly hypertensive patients. The impressive reductions in all major cardiovascular endpoints with nitrendipine-based therapy belie the therapeutic nihilism that, unfortunately, appears to be quite prevalent about the management of this condition and that is based on the mistaken impression that nothing could be done, as isolated systolic hypertension was part of the "normal aging process" with its consequent "hardening or stiffening" of the arteries. It is quite clear, from the results of Syst-Eur, that devastating cardiovascular endpoints can be prevented effectively by appropriate antihypertensive treatment.

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